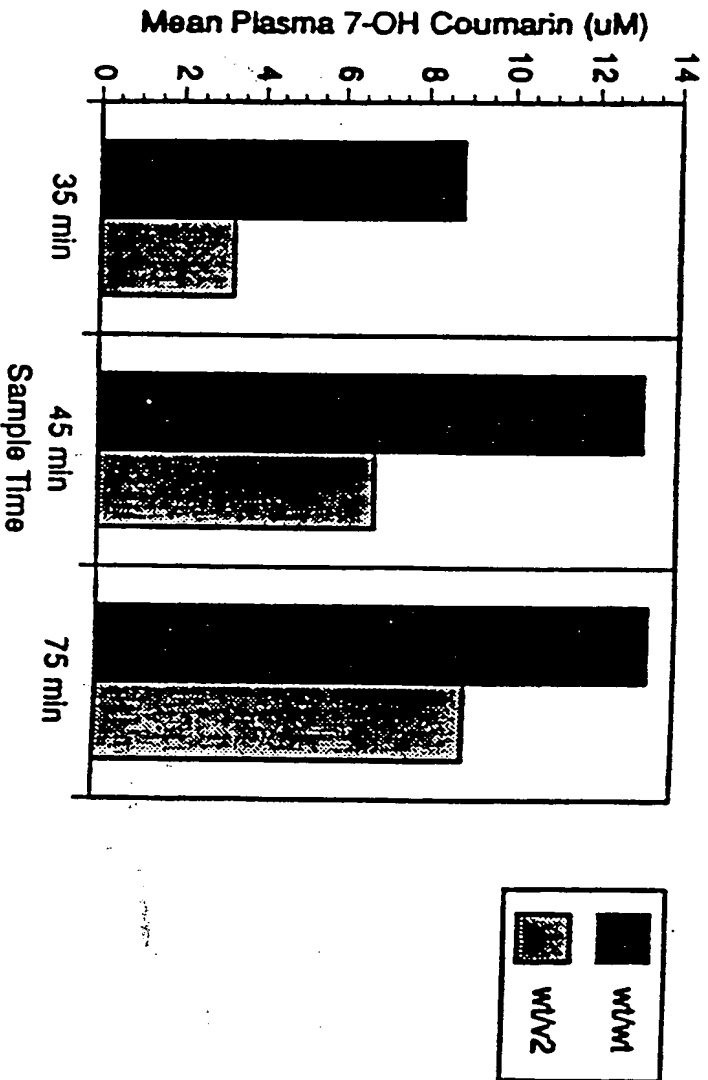


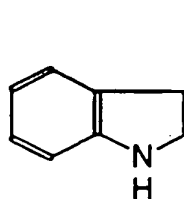
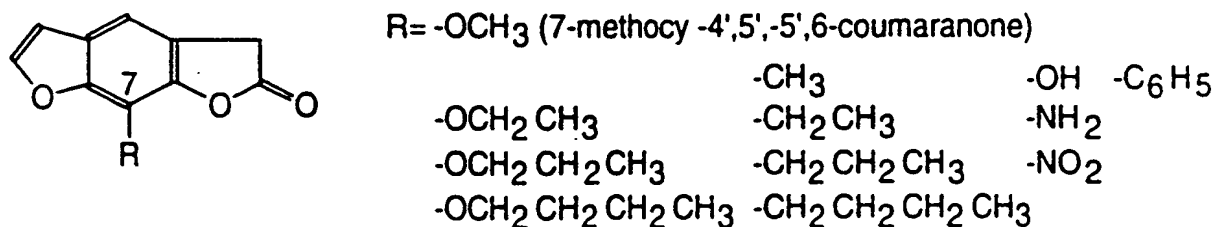
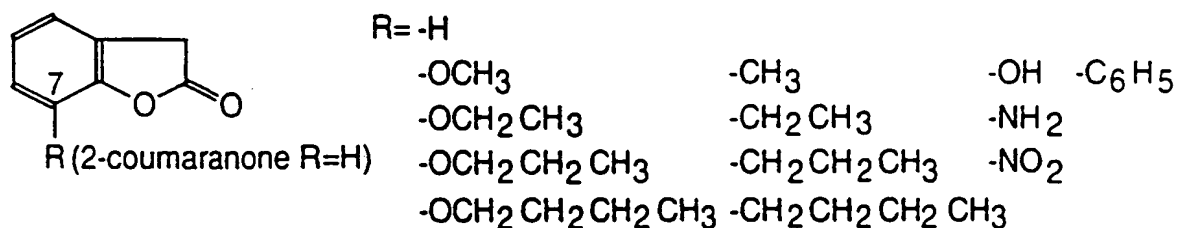
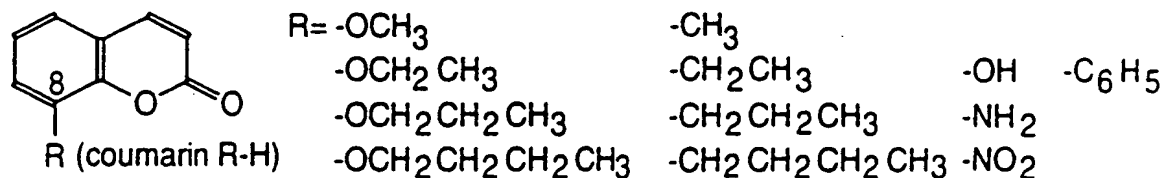
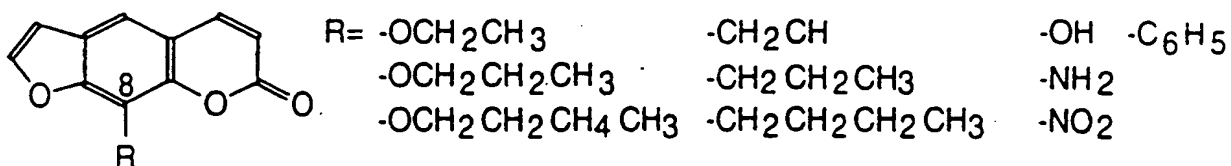
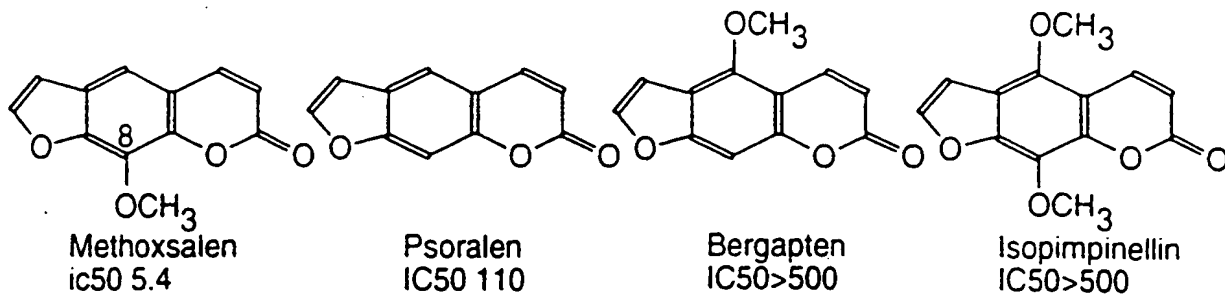
FIGURE 1

Heterozygous CYP2A6 individuals have lower CYP2A6 activity than wild type/wild type (wt) individuals

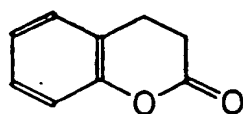


Application of a method to characterize CYP2A6 activity in human subjects by taking plasma samples at times as early as 35 minutes after administration of an oral dose of coumarin (100 mg in this example). Lower doses of coumarin may also be used and the data can also be expressed as a ratio of coumarin/7-OH coumarin. The test can also be performed using oral nicotine or another CYP2A6 substrate.

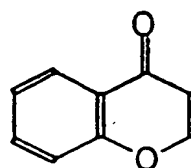
2/23
FIGURE 2A



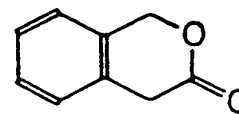
Indole



Dihydrocoumarin

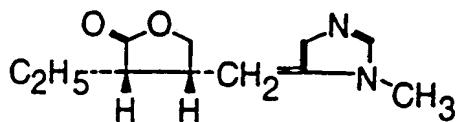


Chomone

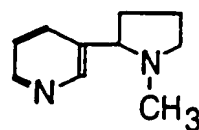


3-Isochromanone

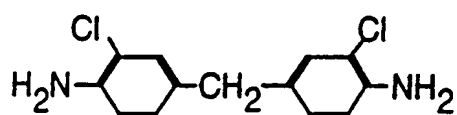
3/23
FIGURE 2B



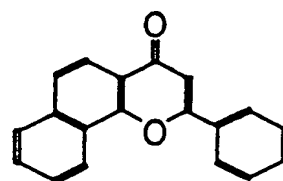
Pilocarpine



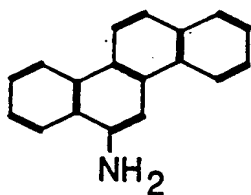
Nicotine



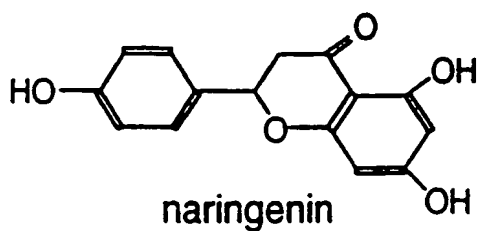
4,4'-Methylene bis[2-chloroaniline]



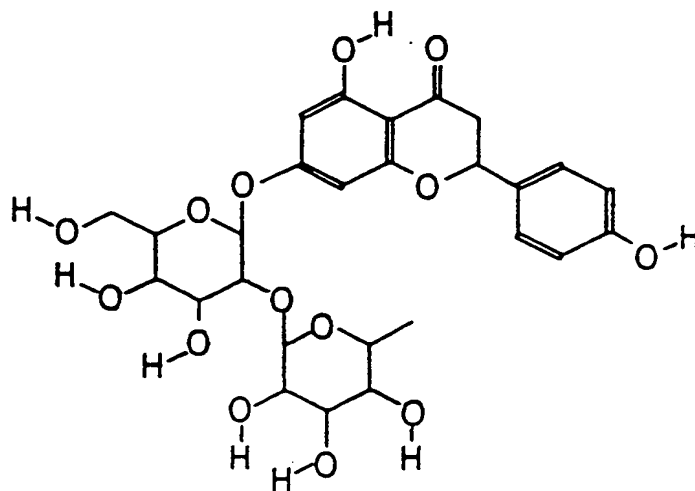
6-Aminochrysene



α-Naphthoflavone

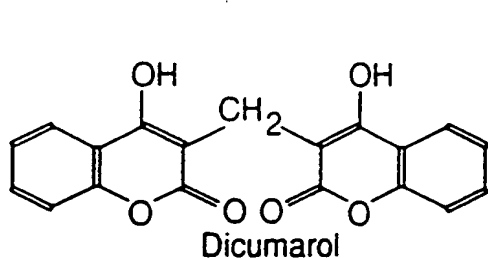


naringenin

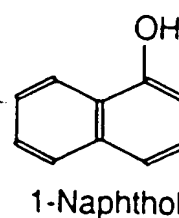
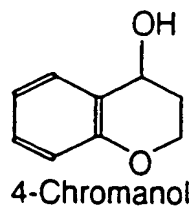
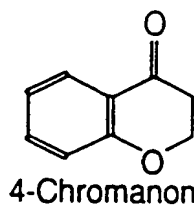


naringin

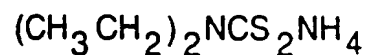
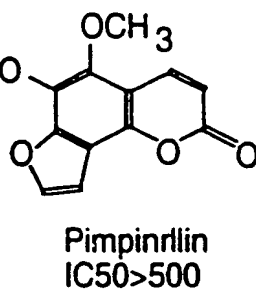
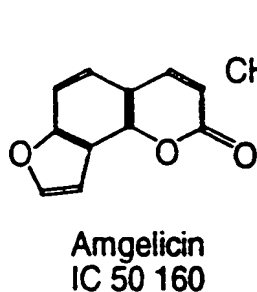
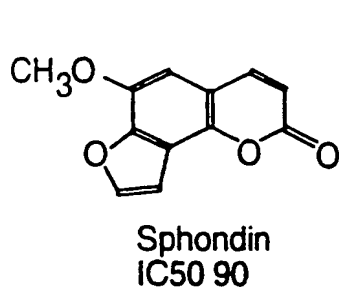
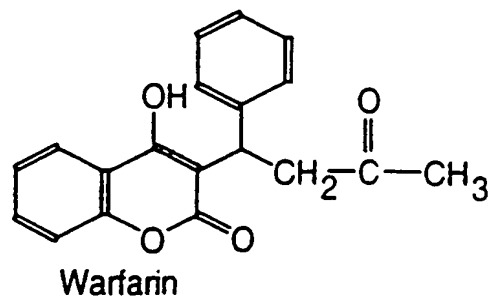
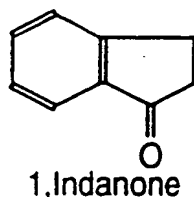
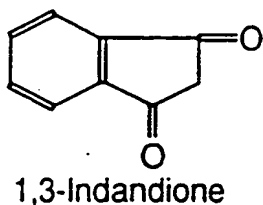
4/23
FIGURE 2C



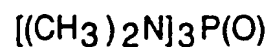
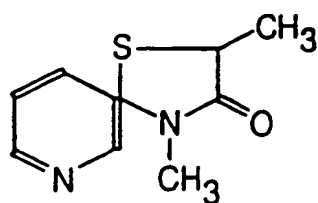
About 80% activity left at 0.05 mM concentration



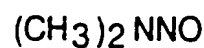
70% inhibition at
 0.5 mM concentration



Diethyldithiocarbamic acid
 ammonium salt



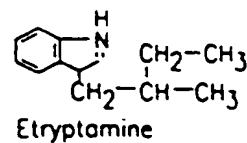
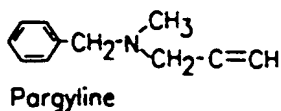
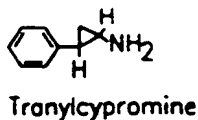
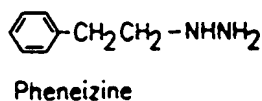
Hexamethylphosphoramide



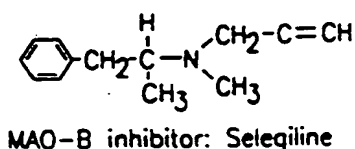
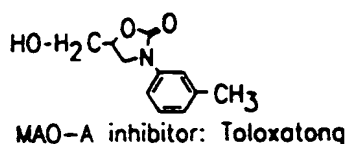
N-Nitrosodimethylamine

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FIGURE 2D

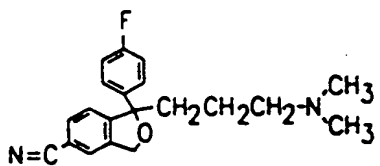
Non-selective MAO inhibitors



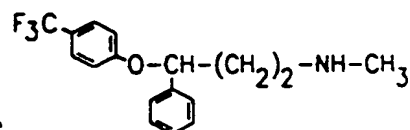
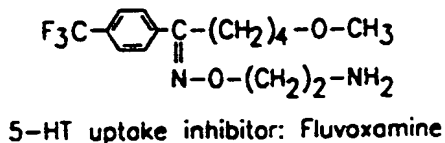
Selective MAO Inhibitors



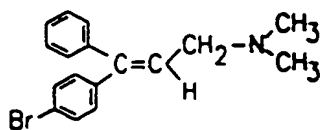
Antidepressants



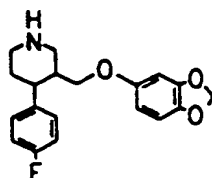
5-HT uptake inhibitor: citalopram



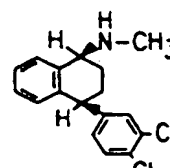
5-HT inhibitor: fluoxetine



5-HT uptake inhibitor: Zimeldine

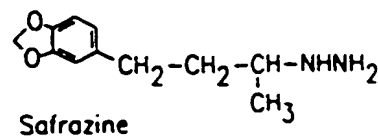
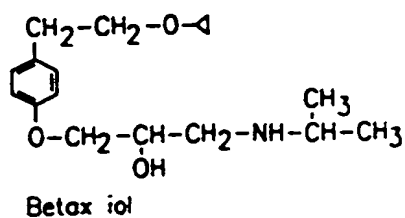
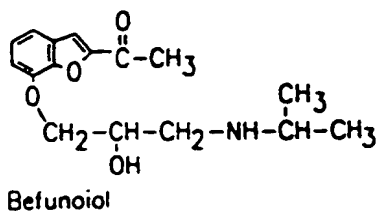
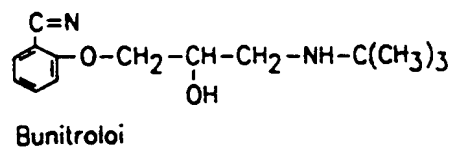
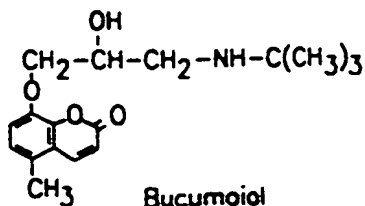
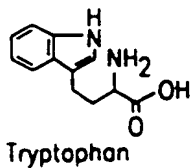


Paroxetine



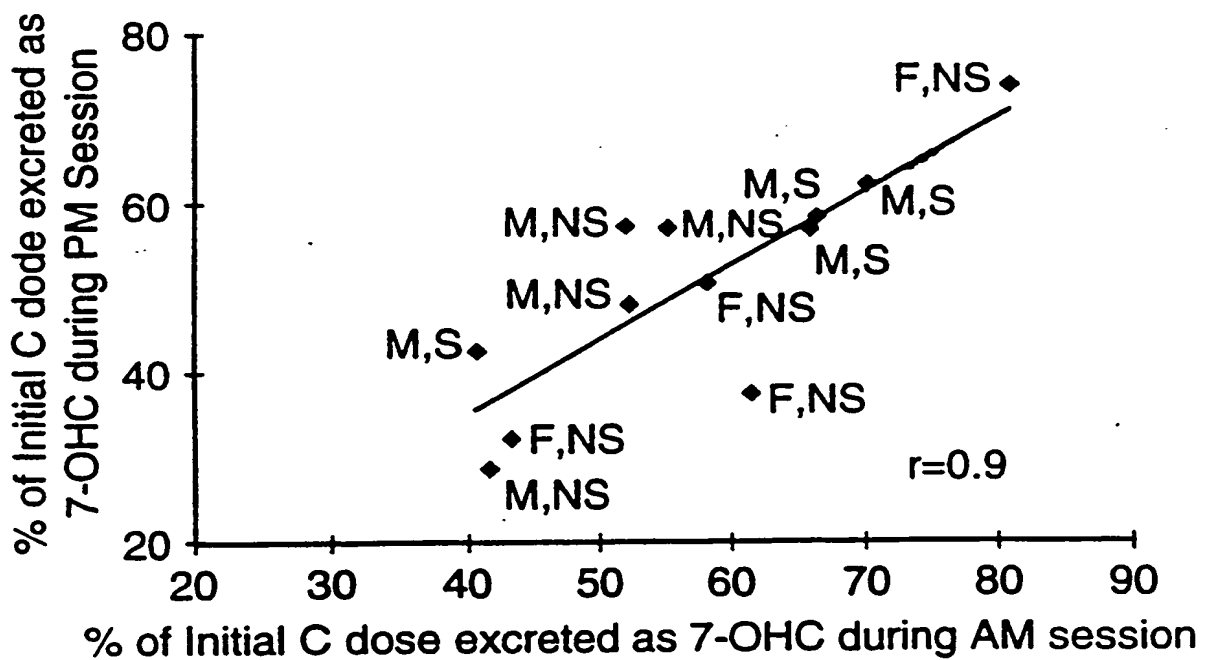
Sertraline

Others

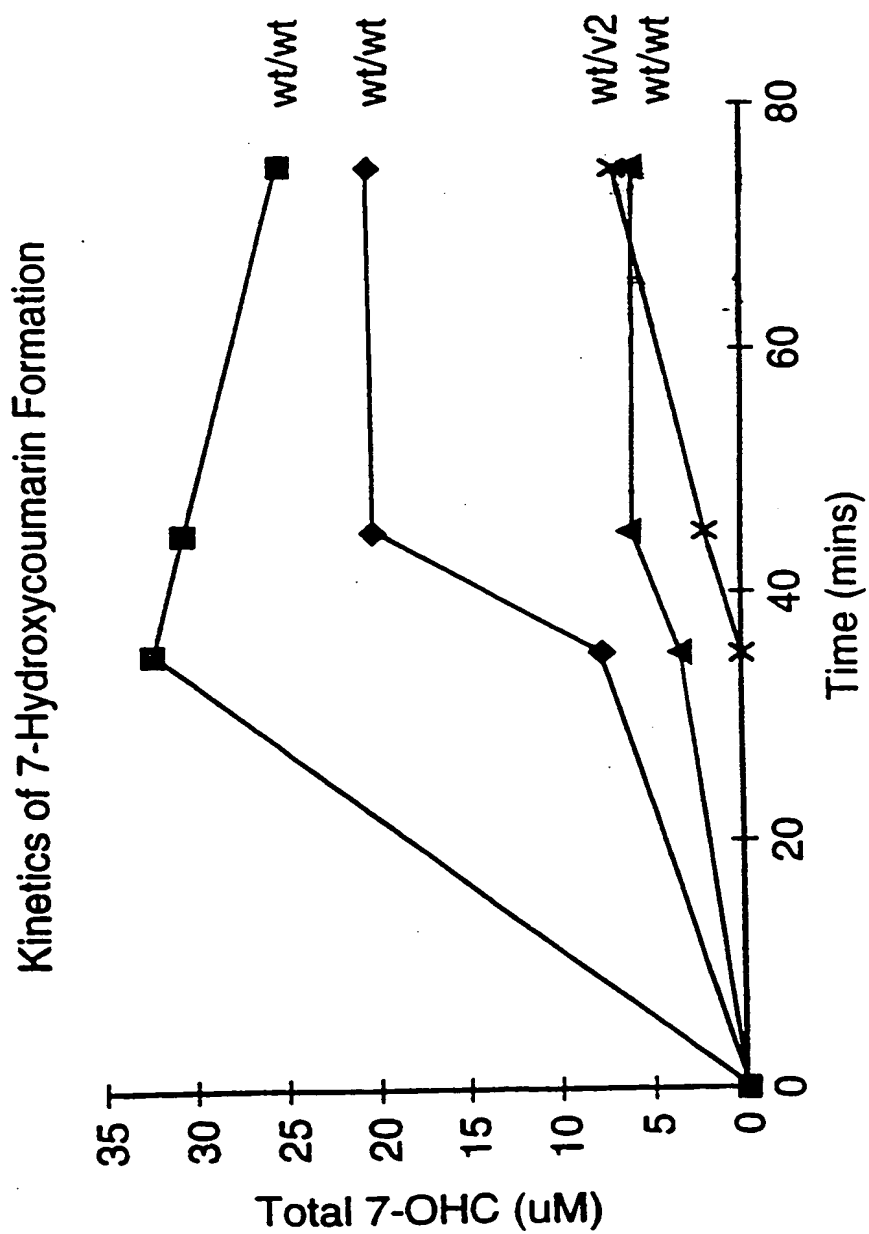


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FIGURE 3

Comparsion Between Morning and Afternoon Testing Sessions.



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FIGURE 4



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FIGURE 5

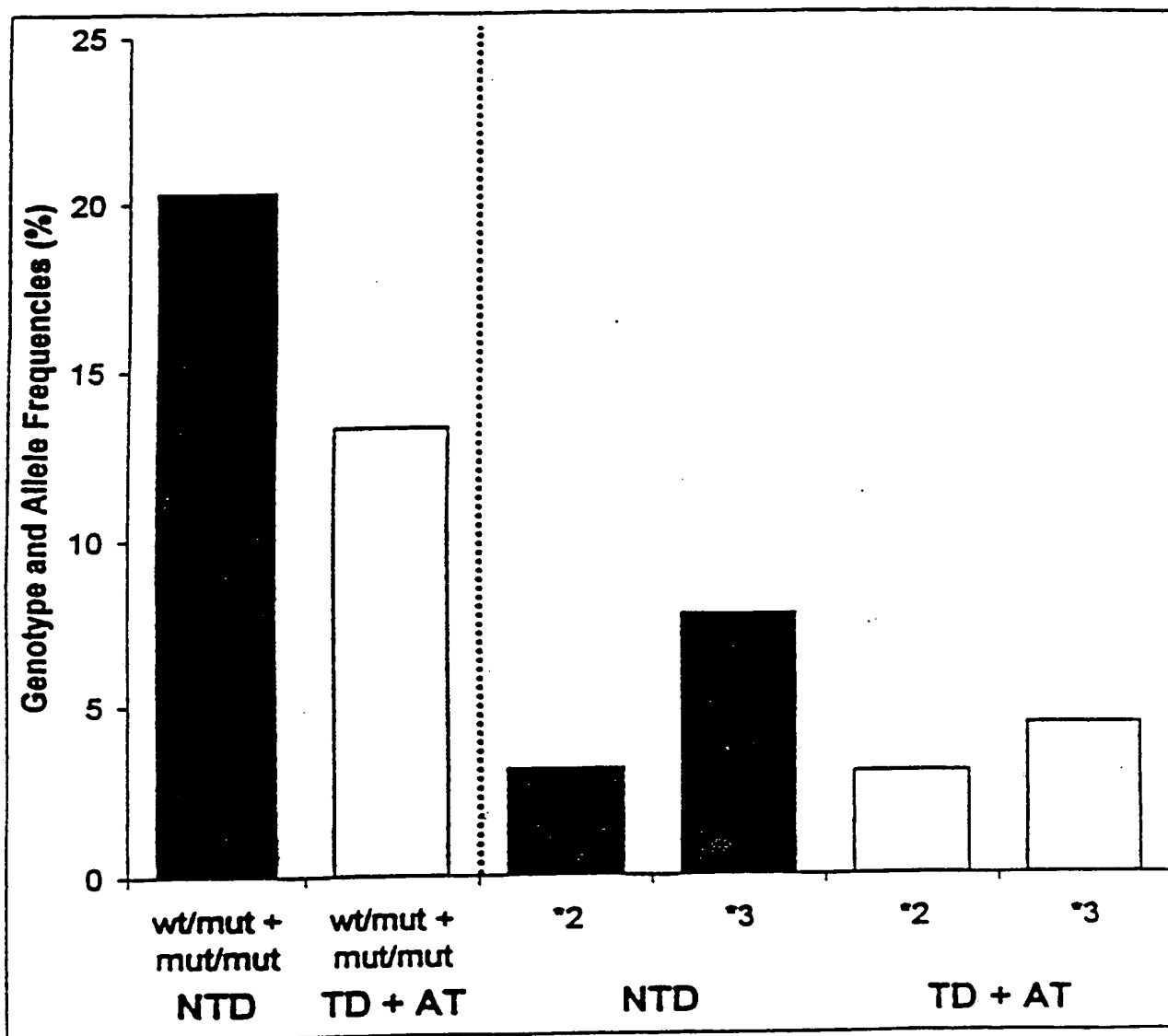


FIGURE 6

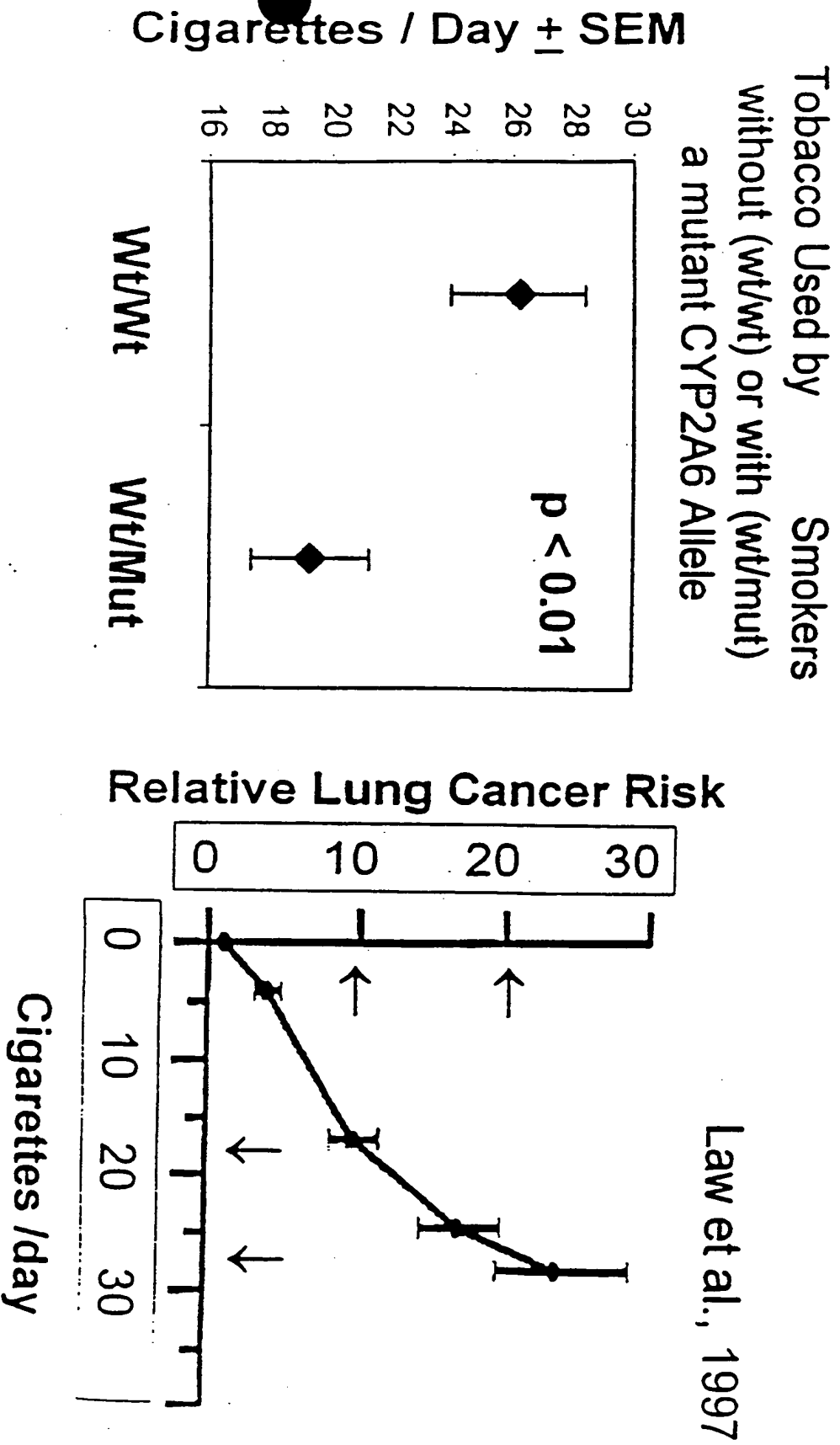


FIGURE 7

Plasma nicotine, ng/ml

Comparison	F	p	Significant drug-vs-drug differences		
Main effect of drug	21.830	0.000	Plac	M 30	T 10
Main effect of sex	1.480	0.252		0.0001	0.0001
Drug*sex interaction	1.250	0.309			

Post-drug mean minus baseline

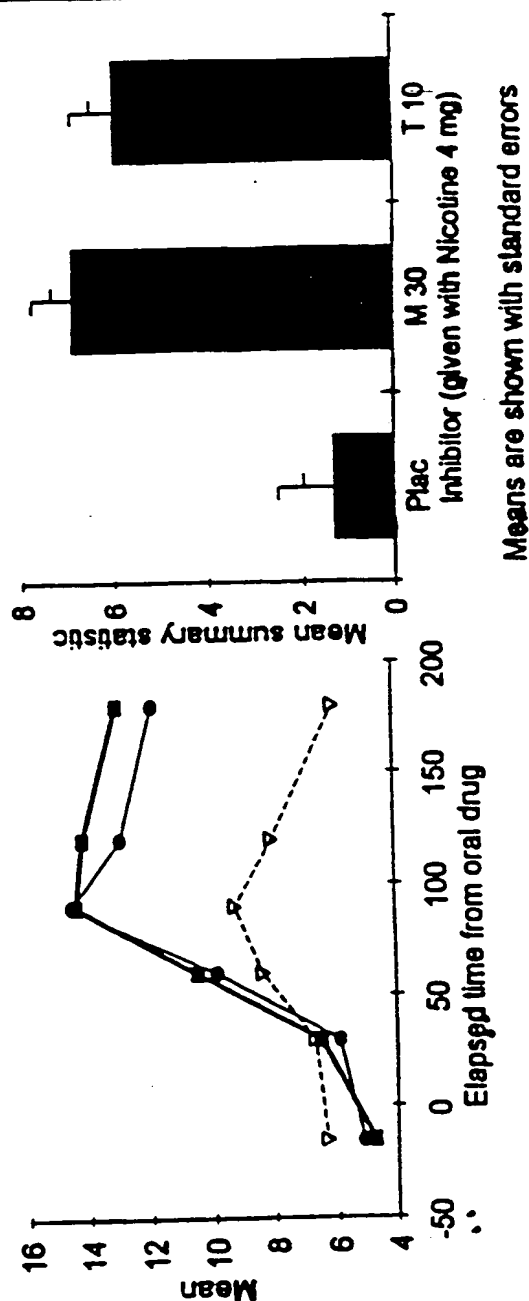
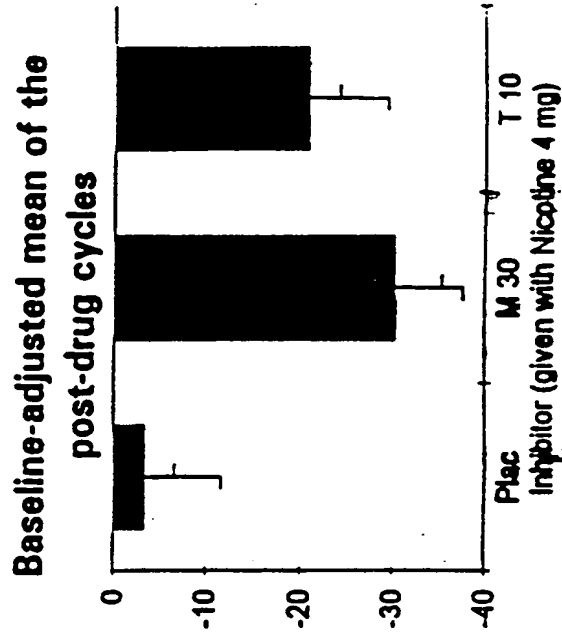
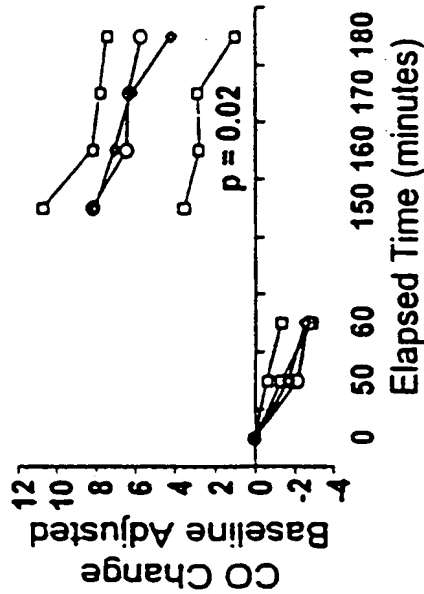


FIGURE 8

Current desire to smoke

Comparison	F	p	Significant drug-vs-drug differences	
Main effect of drug	8.220	0.003 **	M 30	T 10
Main effect of sex	2.190	0.170	Plac	
Drug*sex interaction	3.390	0.054	M 30	0.0171
			T 10	

Baseline-adjusted mean of the post-drug cycles



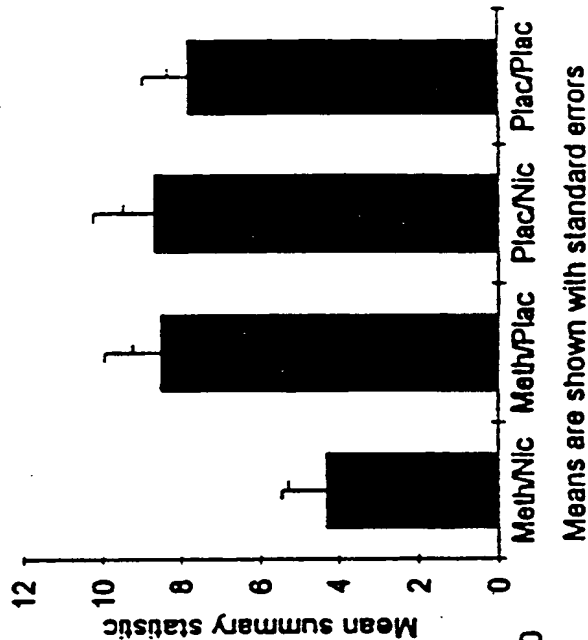
Means are shown with standard errors

FIGURE 9

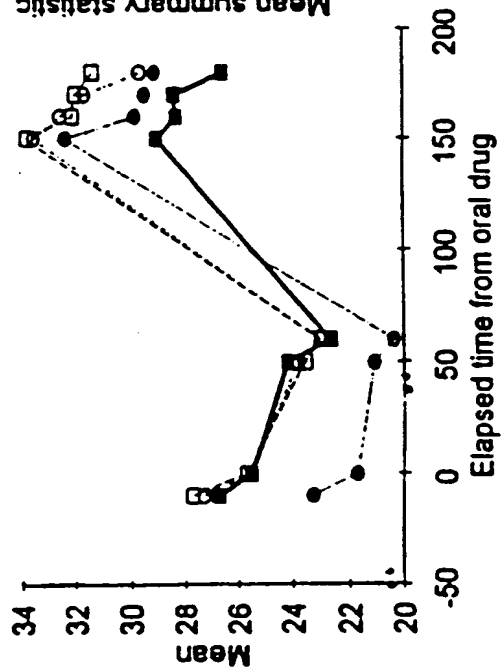
Carbon monoxide, parts/million

Comparison	F	p	Significant drug-vs-drug differences			
Main effect of drug	3.880	0.022 *				
Main effect of sex	0.380	0.554				
Drug*sex interaction	1.370	0.277				
Meth/Nic vs others	11.380	0.003 **	Meth/Nic	0.0078	Plac/Nic	0.0204
			Meth/Plac	0.0082	Plac/Plac	
Among others	0.100	0.904				

Increase during smoking



Means are shown with standard errors



—●— Meth/Nic - - -□- - - Meth/Plac ····●···· Plac/Nic - - -○- - - Plac/Plac

FIGURE 10

Ratio of plasma nicotine increase to CO increase during smoking

Comparison	F	p	Significant drug-vs-drug differences			
			Meth/Nic	Meth/Plac	Plac/Nic	Plac/Plac
Main effect of drug	5.810	0.004 **		0.0039	0.0061	0.0008
Main effect of sex	1.620	0.235				
Drug*sex interaction	0.800	0.506				
Meth/Nic vs others	16.720	0.000 **				
Among others	0.380	0.689				

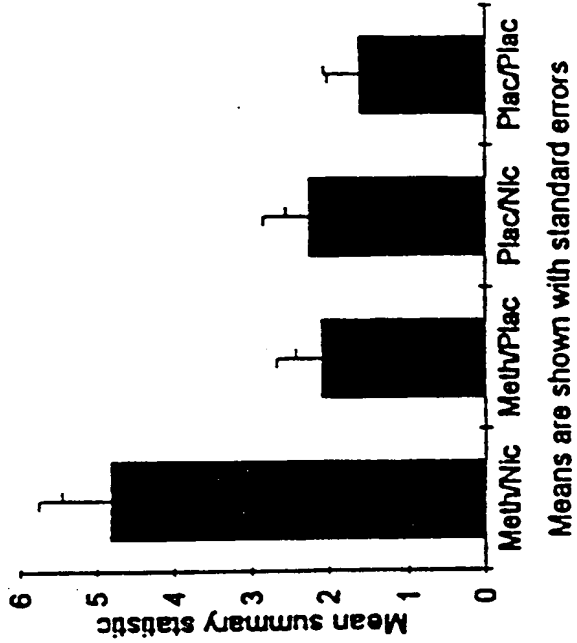


FIGURE 11

Number of cigarettes smoked

Comparison	F	p	Significant drug-vs-drug differences			
Main effect of drug	3.670	0.026 *	Meth/Nic	Meth/Plac	Plac/Nic	Plac/Plac
Main effect of sex	0.470	0.509				
Drug*sex interaction	1.490	0.243				
						0.0032
Meth/Nic vs others	7.510	0.011 *	Meth/Plac			
Among others	1.860	0.177	Plac/Nic			

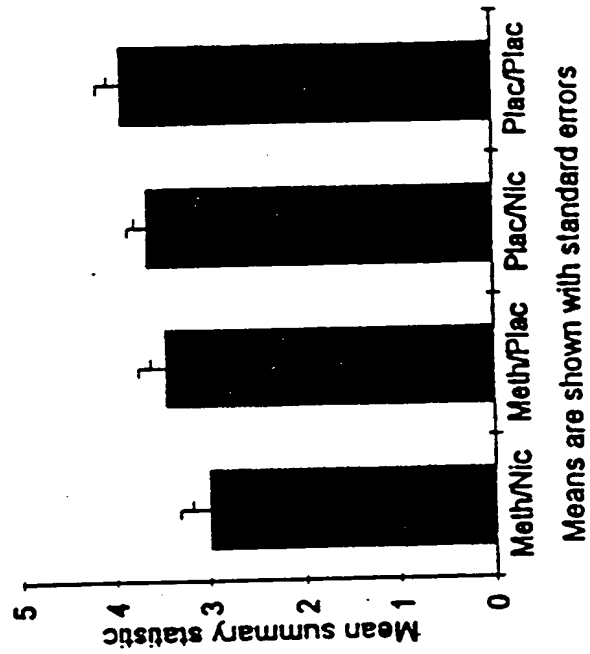


FIGURE 12

Cumulative puffs taken

C mparison	F	p	Significant drug-vs-drug differences
Main effect of drug	3.390	0.035 *	Meth/Plac Plac/Nic Plac/Plac
Main effect of sex	0.760	0.405	
Drug*sex interaction	0.080	0.970	
Meth/Nic vs others	6.340	0.019 *	Meth/Nic
Among others	2.030	0.153	Meth/Plac Plac/Nic
			0.0051

Area under the puff-time curve

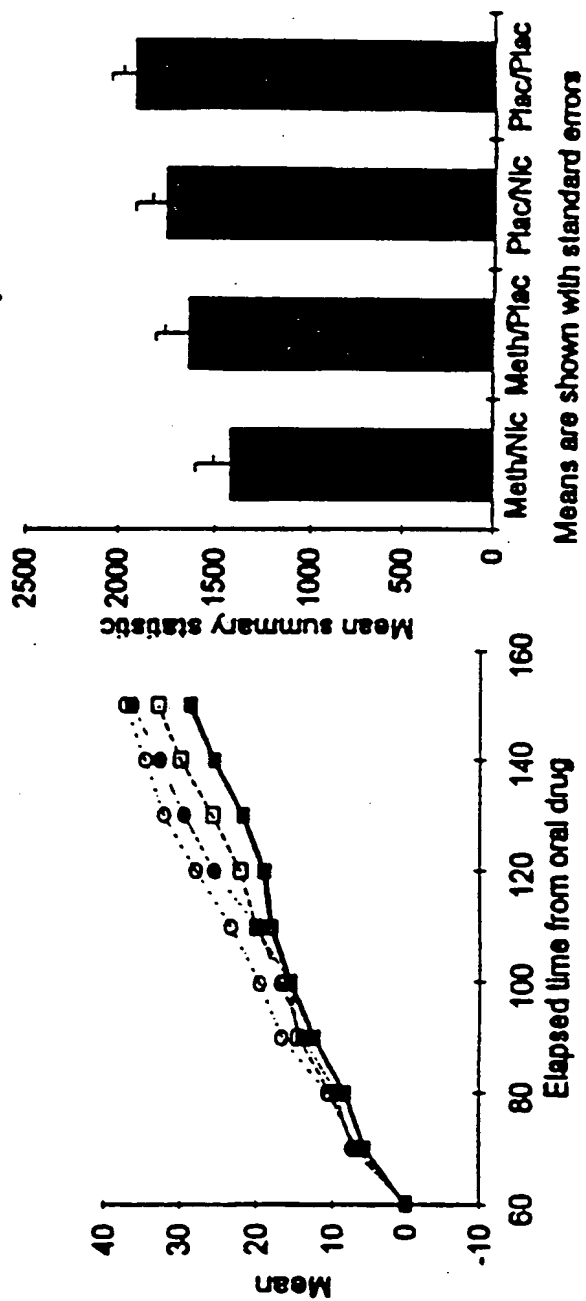


FIGURE 13

Number of grams of tobacco burned			
Comparison	F	p	Significant drug-vs-drug differences
Main effect of drug	3.230	0.040 *	
Main effect of sex	3.290	0.103	Meth/Plac Plac/Nic Plac/Plac
Drug*sex Interaction	1.140	0.355	Meth/Nic 0.0262 Meth/Plac 0.0079 Plac/Nic
Meth/Nic vs others	8.930	0.006 **	
Among others	0.380	0.687	

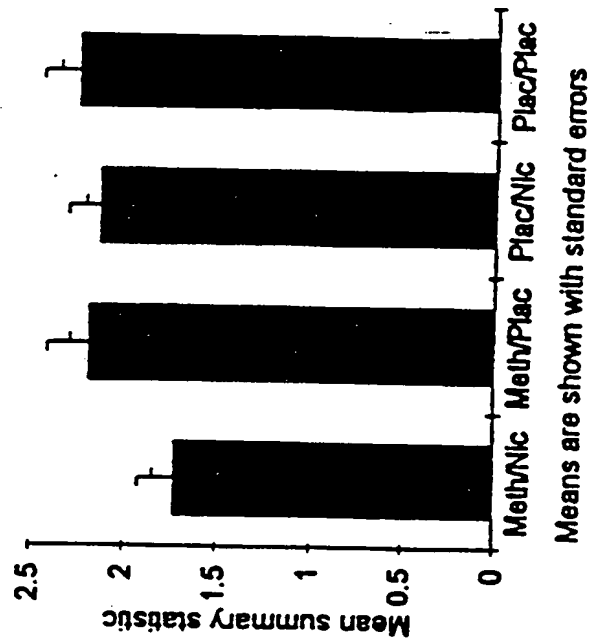


FIGURE 14

Latency between first two cigarettes, minutes

Comparison	F	p
Main effect of drug	2.820	0.060
Main effect of sex	0.810	0.392
Drug*sex interaction	0.170	0.914
Meth/Nic vs others	3.950	0.059
Among others	2.350	0.117

Significant drug-vs-drug differences		
Meth/Nic	Meth/Plac	0.0097
Meth/Plac	Plac/Nic	0.047
Plac/Nic	Plac/Plac	

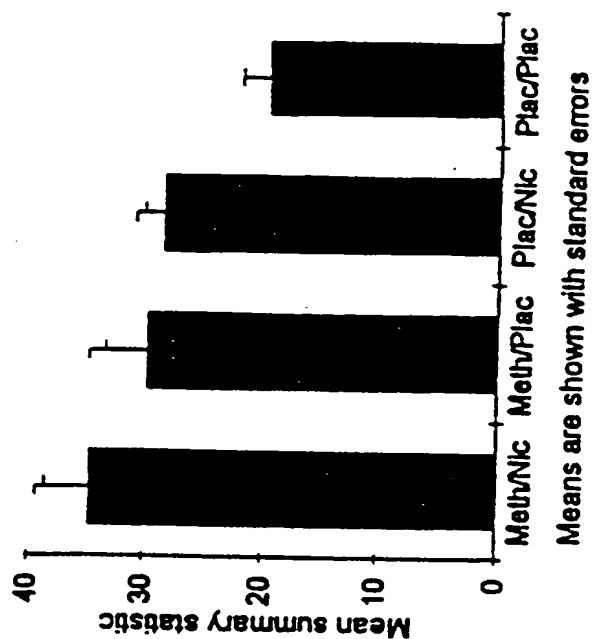
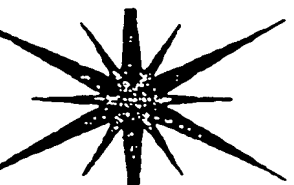
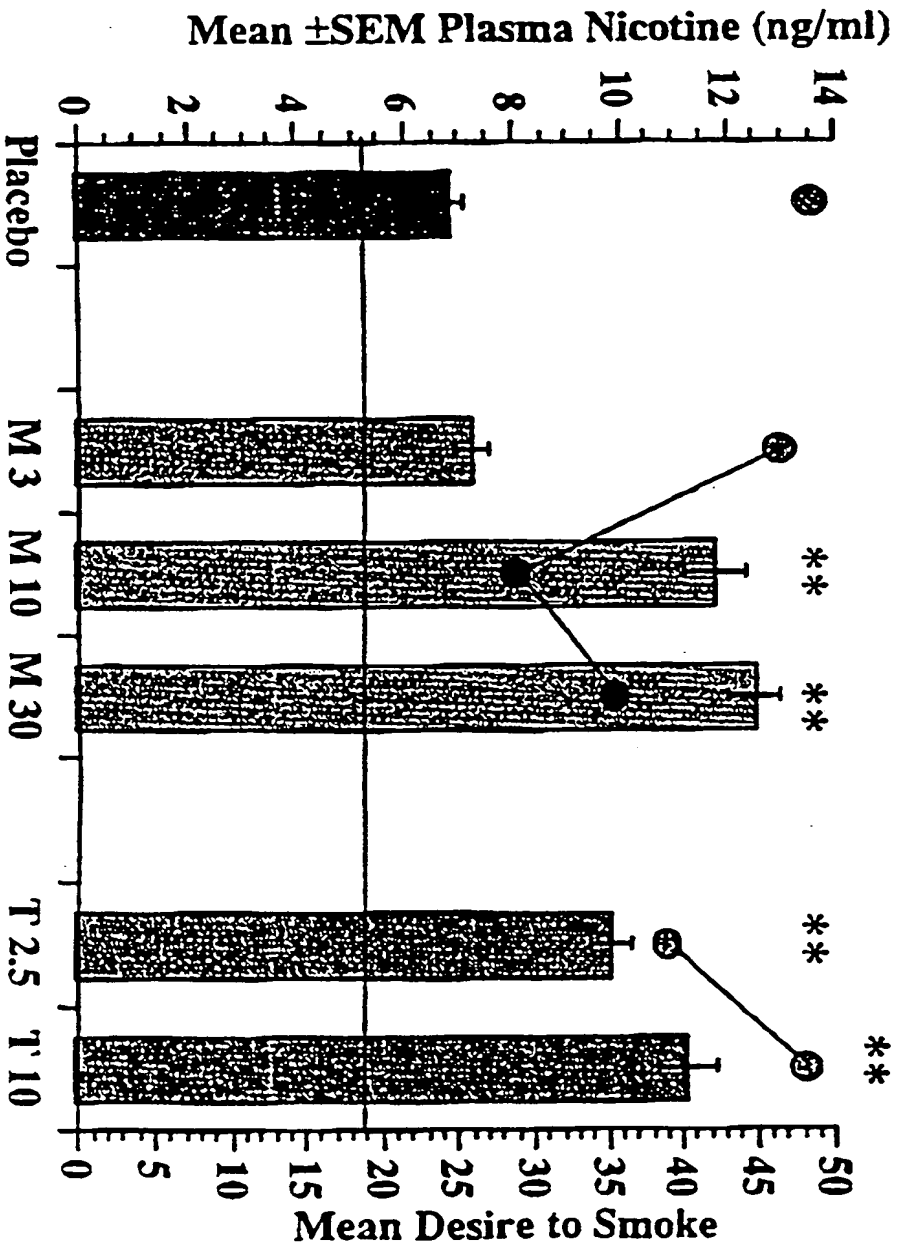


FIGURE 15



Methoxsalen and Translycypromine Increase Oral Nicotine Bioavailability and Decrease Desire to Smoke



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FIGURE 16

Extracts of St. John's Wort Inhibit Nicotine Metabolism in vitro

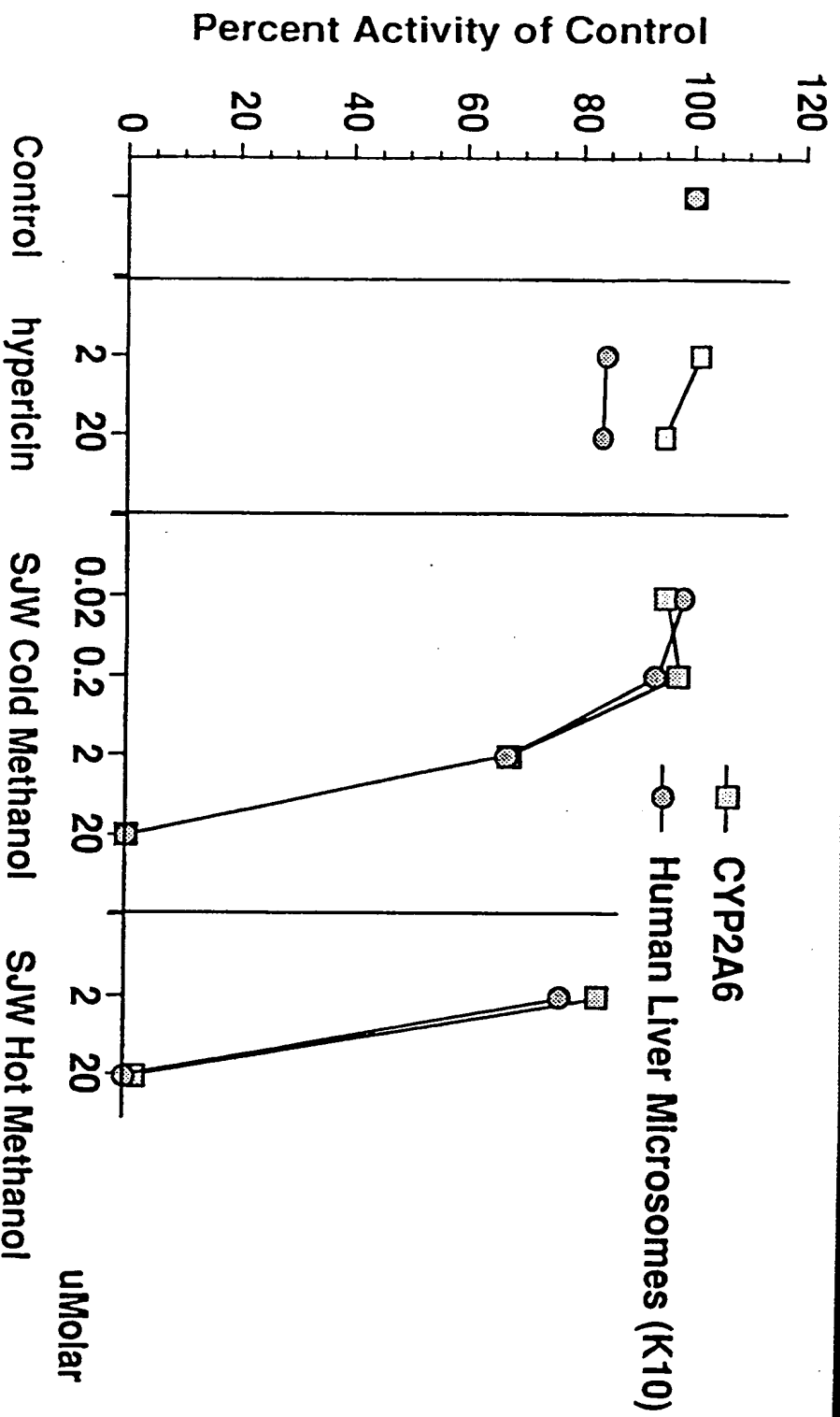
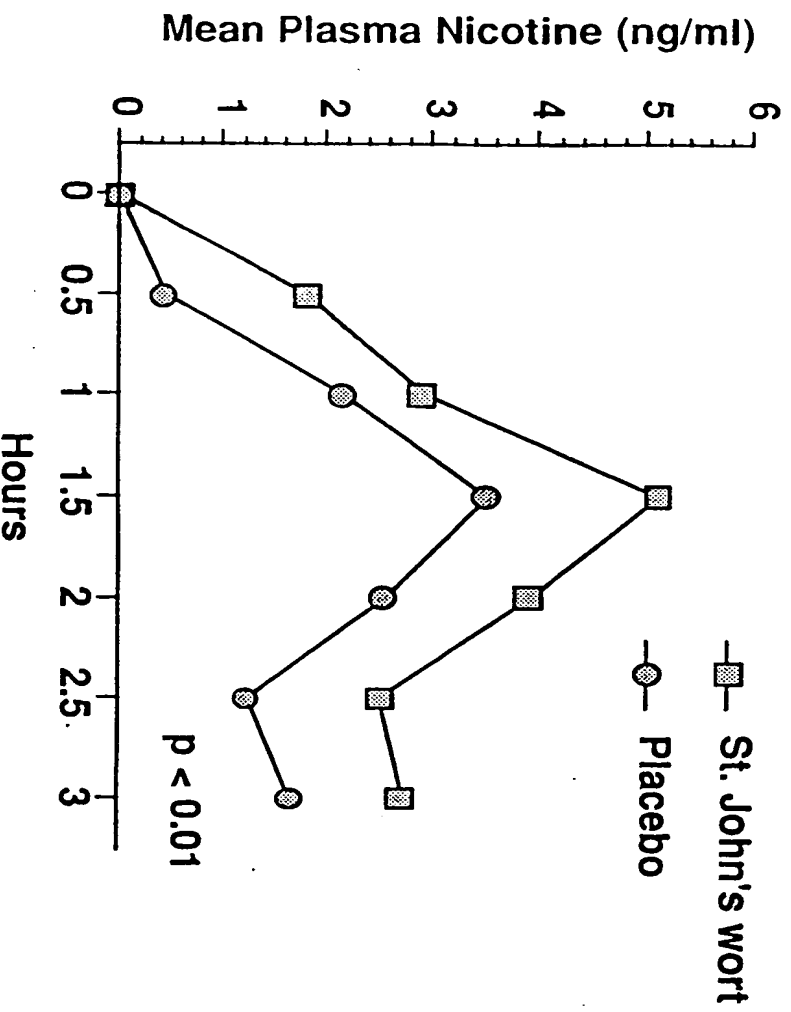


FIGURE 17

St. John's Wort (SJW) Increases Oral Nicotine Bioavailability in vivo



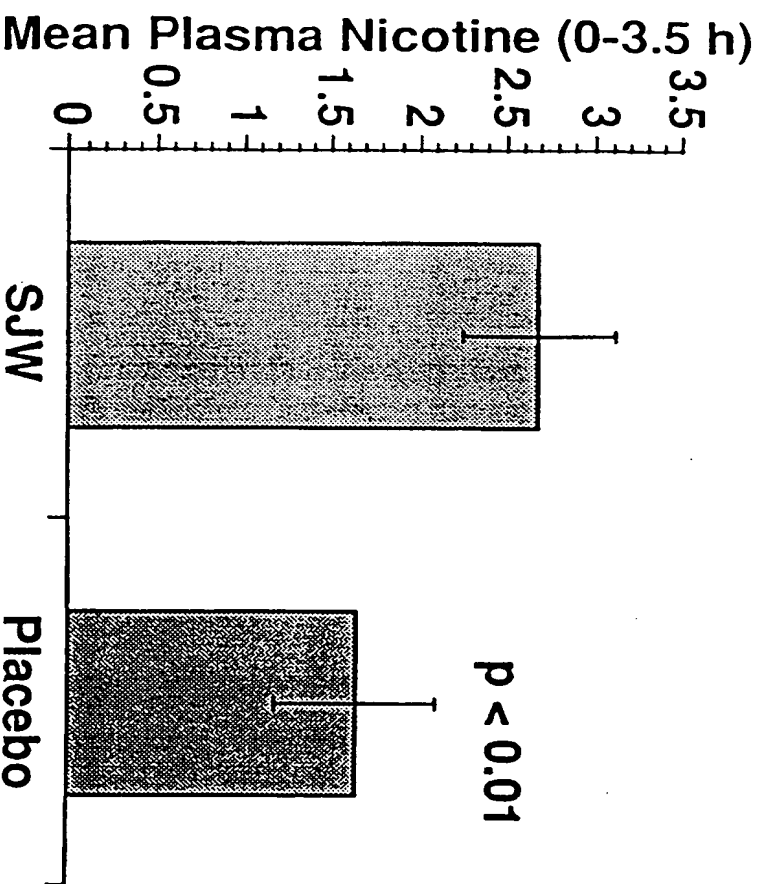
Three St. John's wort 300 mg capsules were taken concurrently with oral nicotine 4.0 mg (base)

Mean plasma nicotine's were 64% higher with SJW

FIGURE 18



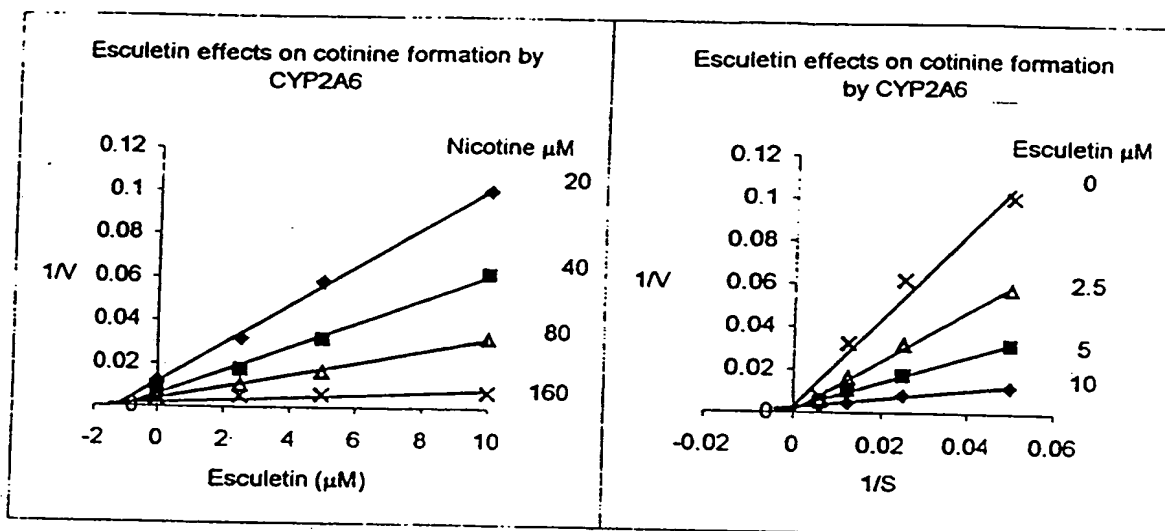
St. John's Wort (SJW) Increases Oral Nicotine Bioavailability in vivo



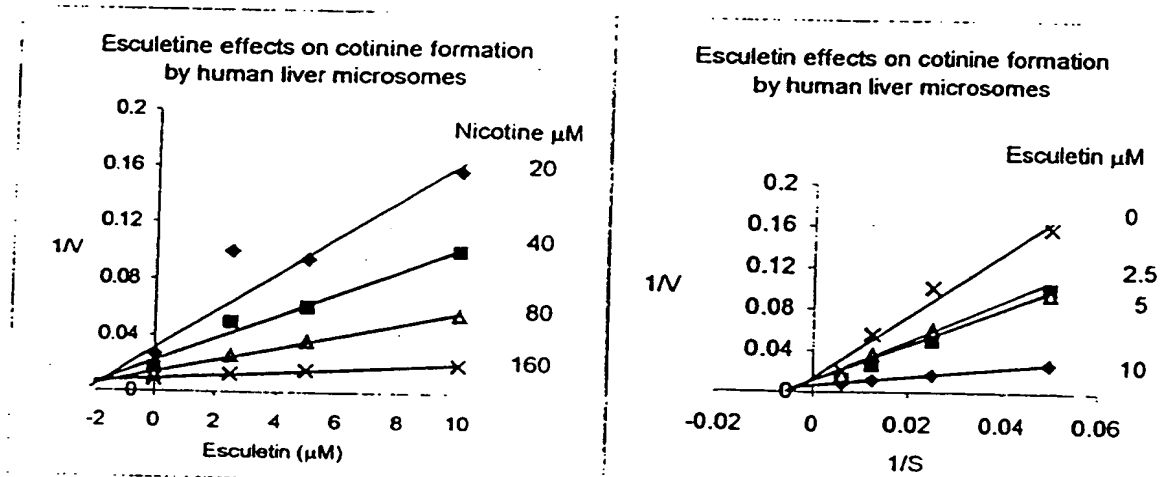
- > Three St. John's wort 300 mg capsules were taken concurrently with oral nicotine 4.0 mg (base)
- > Mean plasma nicotine's were 64% higher with SJW

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FIGURE 19

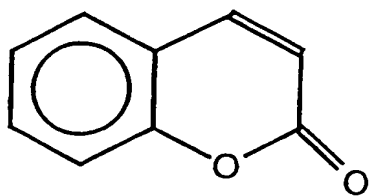


Estimated $K_i = 1 \mu\text{M}$
Calculated by PCS program $K_i = 1.1 \mu\text{M}$

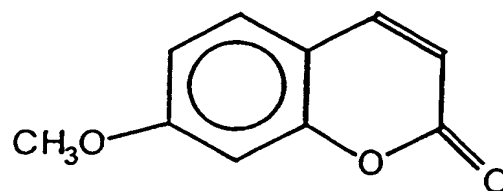


Estimated $K_i = 2 \mu\text{M}$
Calculated by PCS program $K_i = 1.6 \mu\text{M}$

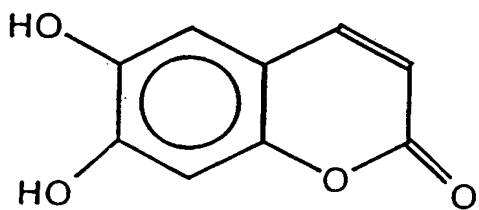
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FIGURE 20



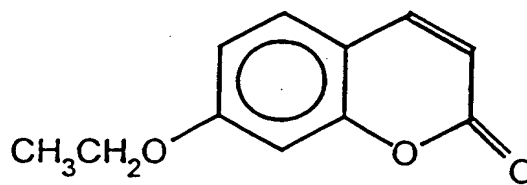
Coumarin



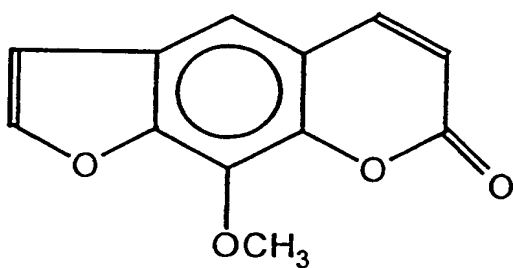
7-Methoxycoumarin



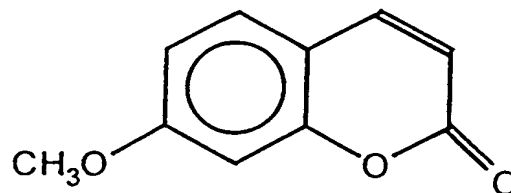
Esculetin



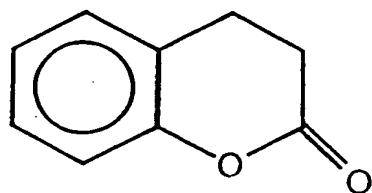
7-Ethoxycoumarin



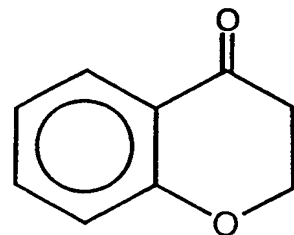
Methoxsalen



7-Methylcoumarin



Dihydrocoumarin



Chromone